

PostScript

LETTERS

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Invasive or non-invasive methods for the diagnosis of subclinical coeliac disease?

I read with great interest the letters published in *Gut* on the role of small bowel biopsies and antiendomysial antibodies (EMA) as methods for diagnosing coeliac disease in patients with iron deficiency anaemia (IDA) (*Gut* 2001;49:595). In particular, Pearce *et al* seem to prefer EMA instead of histological evaluation because of the considerable resource implications for histology departments, and Scott seems to agree with Pearce's affirmation even if he takes into consideration the important role of histological evaluation. However, I do not completely agree with the conclusions of these authors.

Firstly, I would debate the role of non-invasive methods in diagnosing subclinical/silent coeliac disease. In my experience, IDA is the main indication of subclinical forms of coeliac disease¹ and thus it should be taken into consideration in clinical practice. Although EMA are a well known hallmark of coeliac disease and the prevalence is more than 90% in classical forms of coeliac disease, our study and other recent studies clearly showed that the prevalence of EMA (as well as AGA) is lower than expected in clinical practice,²⁻⁴ probably due to the high prevalence of slight histological lesions in these patients (Marsh I-IIa lesions according to the Marsh classification⁵). In contrast, the sorbitol H2-breath test (H2-BT) seems to be more effective than EMA in diagnosing this form of coeliac disease, probably because of a better correlation with slight histological lesions.⁶ In the light of these experiences, sorbitol H2-BT may be a good alternative to small bowel biopsy in identifying coeliac disease in patients with IDA but unfortunately this is not always true. In fact, in clinical practice, it is easy to observe patients with IDA EMA- and a negative sorbitol H2-BT test who show slight histological lesions (Marsh I-II type lesions) with disappearance of IDA and improvement in histology after a gluten free diet (GFD). In these cases the use of non-invasive methods (such as EMA) may be a serious mistake as we may run the risk of not identifying hidden

coeliac disease. These experiences are very important and should be considered in the cost/benefit ratio of diagnosing coeliac disease.

Other important points are the patchiness of the disease, difficulties for pathologists in obtaining biopsies orientated sufficiently, and the cost of small bowel biopsy. Pearce *et al* are not in favour of biopsy. Firstly, many patients suspected of having coeliac disease have upper gastrointestinal endoscopy as an initial investigation which provides an opportunity to perform a biopsy on the second part of the duodenum. Although routine biopsies in all patients undergoing endoscopy would have significant resource implications, endoscopic abnormalities of the second portion of the duodenum associated with coeliac disease have been described,⁷ and these may be used to select patients for biopsy, even if recent studies have re-evaluated the accuracy of endoscopic markers of the disease.⁸ Secondly, multiple biopsy samples obtained from the second portion of the duodenum overcome the problem of the patchiness of the histological lesions (and we routinely take at least six endoscopic biopsies from the descending duodenum). Also, the pathologist's expertise in the Marsh classification of histological lesions in coeliac disease may certainly overcome the problem of incorrectly orientated biopsies. Thirdly, I disagree about the excessive expensive of histological evaluation. In Italy the cost of histological evaluations from a single seat (in this case descending duodenum) is about \$12.40; I do not believe that this is an excessive additional cost to a routine upper gastrointestinal endoscopy.

In light of these considerations, the final question is: should we always perform small bowel biopsies in patients with IDA or other pathologies hiding a subclinical/silent form of coeliac disease? I believe that small bowel biopsy remains the gold standard in diagnosing subclinical forms of coeliac disease (such as IDA), even if the sorbitol H2-BT test is promising as a non-invasive method⁹: the sorbitol H2-BT test seems to be more promising in the follow up of the disease after a GFD (unpublished data). It remains to be determined whether serological testing for antibodies to antitissue transglutaminase improves the diagnosis in cases of mild mucosal lesions. I think that patients at high risk for coeliac disease (such as those with unexplained IDA) should always undergo duodenal biopsy. The costs could be quite high due to the high number of endoscopies that need to be performed but is cost/effectiveness if we consider the significant proportion of patients with coeliac disease who may be missed if screened by serology alone.

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Authors' reply

We would like to thank Dr Tursi for his comments. We suggest that Dr Tursi's and our opinions on the use of antiendomysial antibodies (anti-EMA) and duodenal biopsy (DDB) in the management of coeliac disease are convergent.

We agree that at present anti-EMA can be a flawed diagnostic test and its results must be treated with caution. However, we believe that there is potential for close to 100% sensitivity and specificity, as has been obtained in some laboratories.^{1,2} This highlights the fact that there is a difference in accuracy between centres due to the nature of the test, as discussed in our first letter (*Gut* 2001;49:595). The reasons for these differences are not always easily addressed and may be related not just to the laboratory itself but also to the local population. In centres that have 100% accuracy in anti-EMA testing for coeliac disease, it is clear that its use in the management of coeliac disease will be different in centres that achieve much lower accuracy, some of which are cited in Dr Tursi's letter.

In our letter we were attempting to raise the question as to whether DDB should be obtained in all patients with suspected coeliac disease, and to suggest that if anti-EMA is as accurate as pooled published data, suggesting sensitivity and specificity of 94% and 98%, respectively,^{3,4} theoretically it could be used as a firstline investigation. To put this in context, at present in our biochemistry laboratory, in a hospital serving 550 000, 400 anti-EMA tests are performed per month. Currently at our hospital there is not the capacity to perform 400 extra duodenoscopies each month, and if there were a clinical need, the department would have to be reorganised to do so. Anecdotally, other regions of the UK carry out similar numbers of serological tests for coeliac disease diagnosis.

At present in our patient population, anti-EMA is therefore used as a screening tool, and if positive, patients are offered DDB. This is likely to be the case across the country. Our regional teaching centre has formalised this: tissue transglutaminase (tTG) is used as a screening tool, and anti-EMA and subsequently duodenal biopsy are offered to selected patients.⁵ We believe that this approach has merit, although the routine use of tTG lacks confirmation in the clinical setting.

We agree that currently DDB is the gold standard investigation and that at this moment in time, on the basis of current clinical evidence, should be obtained in all patients with positive serology.

Although we are aware of the benefits of other diagnostic methods, such as sorbitol H2 breath testing (H2 BT), this is still a "resource intensive" test; a quick, cheap, and accurate screening test is required. If sorbitol H2 BT, when thoroughly evaluated, was found to be more effective than DDB in the diagnosis of coeliac disease, we would welcome its introduction.

Better education of primary care physicians in anti-EMA testing may also be required. We have become aware that in our region only a minority of patients with positive anti-EMA are biopsied. This situation should be corrected; it has arisen as a result of anti-EMA being available on a direct access basis to primary care physicians. We wonder if the difference between published guidelines, and what is currently practicable, has contributed to some of the confusion.

On the subject of duodenal biopsies, we believe, as discussed in our letter, that at some point in the future its validity as a gold standard should be reviewed. However, we accept it must remain as such until other methods are thoroughly evaluated, hopefully in well designed controlled trials. If performing an endoscopy for iron deficiency, we would certainly accept that it makes sense to biopsy the duodenum.

In summary, the numbers of patients who are tested at present using anti-EMA means that it has effectively become a screening tool for suspected coeliac disease. However, as the gold standard, we believe that DDB should be offered to all anti-EMA positive patients to confirm the diagnosis and other patients in whom the diagnosis is in doubt, which could include patients who are iron deficient but with negative anti-EMA. We suggest that guidelines for the management of coeliac disease should reflect this.

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Intravenous immunoglobulin for recurrent *Clostridium difficile* diarrhoea

I enjoyed reading Kyne and Kelly's therapy update concerning treatments for recurrent *Clostridium difficile* diarrhoea (*Gut* 2001;**49**:152-3). Recurrence after a single episode of diarrhoea can occur in up to 50% of cases¹ and following recurrent bouts further relapse is even more likely. The authors have demonstrated that a serum antibody response to *C difficile* toxin A during an initial attack is associated with protection against recurrence¹ and suggested that intravenous immunoglobulin may be useful in treating refractory recurrent disease. Here I report successful treatment of four adult patients with recurrent *C difficile* infection using intravenous immunoglobulin in order to increase the number of reported cases.

Case No 1

A 77 year old female with chronic obstructive pulmonary disease (COPD), heart failure, and non-insulin dependent diabetes mellitus (NIDDM) developed *C difficile* diarrhoea after treatment for pneumonia with ceftriaxone and clarithromycin. She had recurrence after each of two courses of metronidazole, a one week course, and a tapering course of vancomycin.² Intravenous immunoglobulin (400 mg/kg) was administered and repeated after 21 days; a simultaneous tapering vancomycin course was given. Her diarrhoea quickly settled and there has been no recurrence over the ensuing 10 months.

Case No 2

A 75 year old female with COPD and NIDDM developed *C difficile* diarrhoea after treatment for pneumonia and cellulitis with ceftriaxone, clarithromycin, amoxicillin, and flucloxacillin. Diarrhoea recurred after courses of oral metronidazole, oral vancomycin, and tapering vancomycin. She was treated successfully with two infusions of immunoglobulin at a 21 day interval and tapering vancomycin. There has been no recurrence over eight months.

Case No 3

A 69 year old man underwent emergency repair of an abdominal aortic aneurysm. Peri-operatively he received flucloxacillin, gentamicin, metronidazole, and ceftazidime. *C difficile* diarrhoea recurred after two separate courses of metronidazole and a further week of vancomycin. Diarrhoea resolved with intravenous immunoglobulin given as above and tapering vancomycin. There has been no recurrence after seven months.

Case No 4

An 82 year old female suffered a stroke. *C difficile* diarrhoea developed after treatment with ceftriaxone, metronidazole, and flucloxacillin for pneumonia and PEG site infection. Diarrhoea recurred after initial courses of metronidazole and vancomycin. Diarrhoea resolved with two infusions of immunoglobulin and tapering vancomycin. She was transferred to a nursing home and there has been no recurrence over five months.

Recurrence is commoner in older patients, those with comorbidity, or those receiving

multiple antibiotics.¹ Failure to mount an immunoglobulin response to *C difficile* is associated with recurrence¹ and Kyne and Kelly included passive immunisation with intravenous immunoglobulin among their options for treating recurrence. However, reports of successful use of immunoglobulin in this setting are few. Leung *et al* successfully treated five children with recurrent *C difficile* with immunoglobulin,³ and there is a single report of success in an adult with recurrent *C difficile* diarrhoea.⁴ Intravenous immunoglobulin has also been effective in two adult patients with severe acute refractory rather than recurrent disease.⁵ Normal pooled human immunoglobulin preparations contain significant titres of anti-*C difficile* antibodies.⁵ Although the number of reported patients is still small, it seems that immunoglobulin may be helpful for recurrent *C difficile*. The combination of two doses of immunoglobulin (400 mg/kg) with a tapering course of vancomycin produced lasting clearance of diarrhoea, even when diarrhoea had recurred after tapered vancomycin alone, suggesting the importance of the immunoglobulin. No complications of treatment were observed.

Intravenous immunoglobulin seems a promising adjunct in recurrent *C difficile* diarrhoea. I would agree with Kyne and Kelly that randomised controlled trials are needed to optimise the management of *C difficile* but such studies should include immunoglobulin.

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Surveillance for hepatocellular carcinoma in liver cirrhosis: have programmes improved because patients have?

In their commentary (*Gut* 2001;**48**:149-50), Bruix and Llovet discuss the paper by Bolondi *et al* (*Gut* 2001;**48**:251-9) and emphasise the fact that survival in patients with hepatocellular carcinoma (HCC) is mainly related to tumour stage and degree of liver function impairment at diagnosis. This is most likely true because of the peculiar features of HCC, which almost inevitably arises in the "mine-field" of a cirrhotic liver whose residual function is one of the main factors influencing therapeutic options and prognosis.¹

Nevertheless, a trend towards increased survival after diagnosis of HCC has recently been

observed, although the surveillance programme has not changed over the years (liver ultrasonography and α -fetoprotein determination every six months). As Bruix and Llovet affirm, this increase in survival may be due to advances in diagnosis even in the absence of effective treatment, to the availability of multiple treatment, or both.

However, it must be emphasised that HCC stage (parameter of the tumour) and residual liver function (parameter of the affected patient) are closely related and influence each other, and that both can influence the choice of treatment and prognosis. Therefore, what should improved survival over the years be attributed to since surveillance programmes are only able to detect a minority of "early" HCCs?

Bolondi *et al* analysed the outcome and cost effectiveness of HCC surveillance programmes. They compared the outcome of a cohort of mixed aetiology cirrhotic patients screened by means of biannual liver ultrasonography and serum α -fetoprotein measurement to the outcome of patients whose HCC had been discovered incidentally. They found that there were no significant differences in eligibility for treatment between patients who had been under surveillance and those who had not (although a higher number of patients in the former group had been transplanted). However, survival at three years was significantly better in the group that had been kept under surveillance. Lastly, both liver function and tumour stage were selected in multivariate analysis as predictors of survival.

We recently performed a similar study in a cohort of hepatitis C virus positive cirrhotic patients. We compared clinical parameters, eligibility for treatment, and survival of patients whose HCC had been discovered during a surveillance programme (biannual liver ultrasonography and α -fetoprotein measurement) with patients whose HCC had been incidentally diagnosed.² Although age, serum α -fetoprotein levels, and unifocality of the tumour were no different between the two subgroups of patients, we found that more patients in the group under surveillance were eligible for treatment (32/33 *v* 18/27; *p*=0.003, Fisher's exact test). Moreover, we found that clinical status at diagnosis was better in the group under surveillance compared with patients with an incidental diagnosis of HCC. Lastly, we observed that longer survival was obtained in treated patients, regardless of diagnosis modality or treatment modality. On the basis of these findings, we attempted to determine whether the longer survival observed in the group under surveillance might be due to better basal conditions, or perhaps they were more likely to benefit from treatment due to their improved clinical status. We thus compared patients treated with the same procedures and analysed the results on the basis of modality of diagnosis. We observed that there was no difference in survival between the groups, and that overall most deaths were liver related (72%) rather than tumour related. Both of these points suggested that the better outcome observed in the group under surveillance was due to the better basal conditions of the patients and not to the procedures themselves. Lastly, multivariate analysis showed that liver function, tumour stage, treatment, and HCC surveillance were independent predictors of better survival.

Thus what emerges from our study as well as from that of Bolondi *et al*'s is that survival of HCC patients is mainly linked to preserved liver function. This probably allows patients to undergo treatment even when this is not clas-

sically considered "curative" as even therapeutic options considered "non-curative" have reportedly obtained increasingly positive results in terms of survival.^{3,5} In an era of multimodal therapeutic approaches to HCCs, these findings further support the results of screening programmes performed almost a decade ago on patients with compensated cirrhosis and whose sole options were liver surgery or percutaneous ethanol injections. No differences were reported regarding survival of patients who developed HCC and those who did not, thus emphasising the importance of residual liver function in relation to survival.⁶ Therefore, what probably lies beneath these findings is that improved medical therapy of the complications of liver cirrhosis, increased efficacy of HCC treatment, and better management of treatment induced sequelae have led to better care of the patients. This has likely changed both the type of patients who enter HCC surveillance studies and their therapeutic outcomes.

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Gastric cancer and *H pylori*

We would like to comment on the relationship of chronic *Helicobacter pylori* infection and gastric cardia cancer risk discussed in the recent combined analysis of prospective serological studies presented by the *Helicobacter* and Cancer Collaborative Group (*Gut* 2001;**49**:347-53). It is our opinion that the null association between *H pylori* seropositivity and gastric cardia cancer risk reported in this analysis may have resulted in a large part from the combination of observational studies with (a) different definitions of gastric cardia cancer and (b) diverse subject populations, particularly with respect to the prevalence of gastro-oesophageal reflux disease (GORD), which we

believe may affect the perceived *H pylori*-cardia cancer relationship.

By definition, the gastric cardia represents only the proximal 2-3 cm of the stomach. This small anatomical region can easily be overgrown by tumours that originate from adjacent mucosal sites. Thus in populations where both oesophageal and gastric adenocarcinomas are common, tumours described as "cardia cancers" undoubtedly include a mixture of neoplasms arising from the lower oesophagus as well as the gastric cardia (and perhaps even the more distal stomach). Classification of gastric cardia cancer has been further confused by the inclusion of malignant lesions situated 2-3 cm above the gastro-oesophageal junction in some previous reports.¹

With respect to disease aetiology, adenocarcinoma of the oesophagus appears to be strongly associated with GORD,¹ while adenocarcinoma of the distal stomach has been positively linked with chronic *H pylori* carriage (*Gut* 2001;**49**:347-53). It is therefore not surprising that both GORD and *H pylori* have been suggested as potential risk factors for "gastric cardia cancer". In our opinion, GORD is probably associated with most oesophageal adenocarcinomas and some true gastric cardia cancers whereas chronic *H pylori* exposure appears to be a predisposing factor for most gastric non-cardia adenocarcinomas and some gastric cardia cancers. Additionally, chronic *H pylori* carriage is thought to reduce the risk of GORD associated tumours by lowering the acid content of refluxed gastric contents² while GORD is not thought to affect the risk of *H pylori* associated tumours.

Since 1985, our group has collaborated on multiple studies of oesophageal and gastric cancer in Linxian, China. Residents of this region are known to be at high risk for oesophageal squamous cell carcinoma and gastric cardia cancer, moderate risk for gastric non-cardia adenocarcinomas, and very low risk for oesophageal adenocarcinoma. The *H pylori* seropositivity rate among cancer free adults has been reported as 56%.³ Based on the endoscopic evaluation of nearly 7000 asymptomatic adults in our studies in Linxian, reflux oesophagitis is uncommon in this population. Moreover, no cases of Barrett's oesophagus or oesophageal adenocarcinoma have been histologically confirmed. In contrast, we have detected more than 175 cases of early gastric cardia adenocarcinoma, almost all of which were confined to the 2-3 cm region below the squamocolumnar junction at the time of diagnosis. Other groups have also reported that reflux oesophagitis and its complications are uncommon and that the *H pylori* carriage rates are high among Asian adults.⁴⁻⁶ Therefore, such populations seem well suited to the investigation of *H pylori* and gastric cardia cancer risk, as the potential disease modifying effects of GORD are virtually non-existent. In the combined analysis from the *Helicobacter* and Cancer Collaborative Group (*Gut* 2001;**49**:347-53), our analysis of the pooled data from the three Asian studies revealed a summary odds ratio estimate of 1.67 (95% confidence interval (CI) 1.06-2.64) for *H pylori* seropositivity and gastric cardia cancer risk. Interestingly, each of the Asian studies further reported similar risk estimates for gastric cardia and gastric non-cardia cancers among *H pylori* positive subjects, which suggests that the bacterium's putatively procarcinogenic effects may be uniform throughout the stomach.

In most Western populations, GORD is a relatively common disorder,⁷ while *H pylori* infection is on the decline.^{2,8} In this setting,

estimating the risk of *H. pylori* associated gastric cardia cancer becomes substantially more challenging. Our further analysis of the combined data from the seven western studies alone yielded a summary odds ratio of 0.60 (95% CI 0.38–0.93) for *H. pylori* seropositivity and gastric cardia cancer risk. Because the proportion of oesophageal, gastric cardia, and gastric non-cardia cancers included in these studies cannot be readily determined, we believe that interpreting this risk estimate as showing a protective (or null) association is problematic. Consistent with the discussion offered above, the apparent lack of association between *H. pylori* exposure and gastric cardia cancer in Western populations may be due to an over representation of misclassified GORD associated lower oesophageal malignancies in these studies. The appropriateness of combining the existing Western and Asian studies of *H. pylori* and gastric cardia cancer risk is further called into question by formal statistical testing. When we do a heterogeneity test that allows for potential differences between Western and Asian studies, we find that the odds ratios are significantly different ($p=0.002$).

In summary, we believe that *H. pylori* carriage is a risk factor for adenocarcinoma throughout the stomach, including the gastric cardia. The different conclusion reached by the recently published combined analysis seems likely to have been influenced by pooling data from subject populations with demonstrated or plausible differences in disease classification and disease aetiology, respectively. More specifically, we believe it is difficult to accurately judge the relationship between *H. pylori* seropositivity and gastric cardia cancer risk among populations wherein tumour location has not been rigorously defined and GORD is highly prevalent (due to the potentially misleading biological effects associated with this condition). Thus we respectfully disagree with the conclusion proposed by the *Helicobacter* and Cancer Collaborative Group that "*H. pylori* does not appear to increase the risk of cardia cancer". However, we do agree that additional prospective studies, with larger case numbers and longer follow up intervals, would be useful in clarifying this issue.

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NOTICES

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The European Society for Parenteral and Enteral Nutrition will be hosting its annual meeting on 31 August to 4 September 2002 in Glasgow, UK. The organisers anticipate 300 delegates, principally from Europe but also from the USA and the Far East. Further information: Mrs Pat Howard, Honorary Secretary, BAPEN, Head of Nutrition and Dietetic Services, Bristol Royal Infirmary, Bristol BS2 8HW. Tel: +44 (0)117 928 2049; fax: +44 (0)117 928 3005; email: pat.howard@ubht.swest.nh

Postgraduate Gastroenterology

This course will be held on 15–18 September 2002 in Oxford, UK. The course has been designed for consultants and registrars, including those who do not specialise in gastroenterology. Topics will include: Barrett's Oesophagus; The Case for Endoscopic Surveillance Debate; Liver Disease; Bacteria and the Gut; IBD Therapeutics, Gastrointestinal Bleeding, Endoscopic Training. Further information: Professor Derek P Jewell, University of Oxford, Nuffield Department of Medicine, Gastroenterology Unit, Gibson Laboratories, 2nd Floor, Radcliffe Infirmary, Block 21, Woodstock Road, Oxford OX2 6HE. Tel: +44 (0)1865 224829; fax: +44 (0)1865 790792; email: derek.jewell@ndm.ox.ac.uk; website: www.medicine.ox.ac.uk/gastro

British Association for the Study of the Liver

The 2002 BASL meeting will be held on 11–12 September in Newcastle, UK. Further information: Mrs Jackie Carter, Centre for Liver Research, University of Newcastle, Floor 4, William Leech Building, Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK. Tel: +44 (0)191 222 5640; fax: +44 (0)191 222 0723; email: j.a.carter@ncl.ac.uk

3rd World Chinese Congress of Digestology

This congress will take place on 23–25 September 2002 in Beijing, China. Further information: Lian-Sheng Ma, President of WCCD, PO Box 2345 Beijing 100230, China. Fax: +86 6589 1893; email: wqjd@public.bta.net.cn

EPGS Second Update on Coloproctology

The European Postgraduate Gastro-Surgical School presents this course on 10–11 October 2002 in Amsterdam, the Netherlands. Further information: visit the website www.epgs.nl, or email epgs@amc.uva.nl. Tel: +31 20566 3926/4386.

Xth European Course on Therapeutic Digestive Endoscopy and Radiology

This course will take place on 24–25 October 2002 in Rome, Italy. Further information: SC Studio Congressi, Via Francesco Ferrara 40, 00191 Roma, Italy. Tel: +39 06 3290150; fax: +39 06 36306897; email: sc.congressi@stm.it; website: www.scstudiocongressi.it

Advances in the Inflammatory Bowel Diseases

This conference will take place on 6–7 December 2002 in New York, USA. Further information: Heather Drew, Imedex, 70 Technology Drive, Alpharetta, GA 30005-3969, USA. Tel: +1 770 751 7332; fax: +1 770 751 7334; email: h.drew@imedex.com; website: www.imedex.com

15th European Intensive Course (SMIER) Digestive Endoscopy

This course will take place on 16–17 December 2002 in Strasbourg, France. Further information: Michele Centonze Conseil, 6 bis Rue des Cendriers, 75020 Paris, France. Tel: +33 1 44 62 68 80; fax: +33 1 43 49 68 58.